
Cardiovascular Effects of Potential Occupational Hazards

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Cardiovascular effects of potential occupational hazards have received relatively little attention. The major inhalant occupational exposures of concern are carbon disulfide, nitrates, halogenated hydrocarbons and carbon dioxide. Occupational exposure to certain trace metals may also be associated with adverse cardiovascular effects. Of concern is potential toxicity from cobalt, antimony, lead, cadmium and arsenic. Potential physical hazards exist in association with noise, heat and radio-

frequency radiation. In most instances, the data are suggestive rather than conclusive. Further epidemiologic studies with careful control for potentially complicating factors, such as baseline differences in blood pressure, cigarette smoking habits and age, are needed. In some areas where epidemiologic studies have provided clues, the mechanisms of action of potential occupational hazards require further basic scientific investigation.

Surprisingly little medical or public health attention has been given to the cardiovascular effects of potential occupational hazards (1). The recent emphasis on occupational disease has focused on chemical carcinogenesis and lung disease, even though cardiovascular disease accounts for more than 50% of all deaths in the United States, whereas cancer and lung disease account for approximately 15% each. Occupation-associated cardiovascular disease is a public health problem for which the risk factors have not yet been delineated fully. Furthermore, the overall magnitude of the problem has not been defined. Although mental stress has been associated with serious cardiac arrhythmias (2), including sudden death (3,4), risk factors other than lifestyle may have a much greater impact.

This review will refer to lifestyle stress and physical activity, but will emphasize more tangible associations between certain occupations and cardiovascular disease, particularly exposure to certain inhalants and trace metals as well as physical stresses imposed in the workplace. Unfortunately, most of the data derived from study in these areas are suggestive rather than conclusive. Although certain occupations are associated with a high risk of cardiovascular disease, the possible mechanisms of action for these occupational dangers are, in most cases, poorly understood. Thus, not only is further epidemiologic study needed, but

the clues obtained from previous epidemiologic studies require further investigation in the basic science laboratory.

One major difference between occupation-associated cardiovascular disease and other forms of cardiovascular disease is that potential risk factors for occupation-associated disease usually cannot be controlled or modified by the individual worker or physician. In contrast, when considering coronary artery disease, for example, the individual patient can consciously decide to discontinue smoking cigarettes and the individual physician can aggressively treat a patient's hypertension. Both of these measures will reduce substantially the risk of coronary artery disease. However, in occupational medicine, an individual worker's or physician's efforts may be inadequate.

Inhalant Occupational Exposures

Carbon disulfide. Of the various types of occupational exposure to inhalants that are associated with cardiovascular disease, probably the best documented is carbon disulfide exposure. More than 500,000 workers in the United States are exposed to carbon disulfide, which is essential to the manufacture of rayon and carbon tetrachloride (5,6).

In 1968, a mortality study of viscose rayon workers was reported from the United Kingdom (7). In this investigation, it was found that the death rate from coronary heart disease was 2.5 times greater among men in the rayon industry who had been exposed to carbon disulfide for more than 10 years than among other workers. A group of Finnish investigators (8) undertook a case control study to determine the cardiovascular effects of working in rayon manufacturing plants.

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Among 343 men exposed to carbon disulfide, 14 died of coronary heart disease within the 5 year period of follow-up. In comparison, only 3 of 343 men in the control group died (probability $[p] < 0.007$). Thus, the relative risk of a fatal myocardial infarction was 4.8 times greater among those exposed. In a subsequent study (9), these researchers adjusted their original relative risk estimates for the potentially confounding effects of hypertension and aging. After these adjustments were made, carbon disulfide exposure was found to yield a relative risk of 2.3 for coronary disease mortality.

Nitrate withdrawal (explosives). For the past 30 years, it has been recognized that abrupt withdrawal from nitrates can cause sudden death (10,11). This syndrome has the graphic description of "Monday morning death." Munitions workers become habituated to nitroglycerin and other nitrates used in the manufacture of explosives. After the Friday workday, these workers suddenly are not exposed to nitrates, and over the weekend, this abrupt withdrawal from nitrate exposure places them at risk for cardiovascular death and nonfatal anginal attacks (12-15). It is possible that workers who manufacture nitrates for the pharmaceutical industry are at similar risk.

A particularly interesting report on nitroglycerin exposure comes from investigators at the University of Wisconsin (16). In 1966, certain manufacturing processes at a munitions facility in south central Wisconsin involved the handling of a 35% nitroglycerin-cellulose mixture as it was being converted into solid rock propellant. From 1967 to 1971, approximately 200 workers were exposed. Of these, 160 were women who tended to perform routine work, including most of the handling of the nitroglycerin. In contrast, the 40 men tended to have supervisory roles or machine maintenance tasks. Within 1 to 4 years after exposure, eight women and one man began to exhibit signs and symptoms of ischemic heart disease. These workers developed nonexertional chest pain syndromes, relieved either by nitroglycerin or by returning to work after the weekend.

Coronary angiography was performed in five of these nine patients. No obstructive lesions of the coronary arteries were found in any of these five patients. In one patient studied while in the withdrawal state, coronary artery spasm was demonstrated and was readily reversed by sublingual nitroglycerin. Almost all the patients in this study were premenopausal women who worked in closer contact with the nitroglycerin than did the men.

Halogenated hydrocarbons. Trichloroethylene (17-21) and the fluoroalkanes (22-26) (more commonly known as freons) have been the halogenated hydrocarbons most often implicated in causing cardiac arrhythmia. During the late 1960s, at least 110 healthy adolescents died unexpectedly minutes after they inhaled the propellant freon gases discharged from aerosols (22). Spurred on by these clinical

observations, freons were studied in laboratory animals and were found to cause cardiac arrhythmias (23-26).

However, one need not be a fluoroalkane abuser to suffer from occupational fluoroalkane toxicity. Perhaps the best clinical study of the hazards of fluorocarbon exposure was carried out by Speizer et al. (27) in 1975 when they learned that a group of residents in pathology were experiencing repeated episodes of palpitation. When these subjects were interviewed, it became clear that none of the first year residents experienced palpitation, while the onset of palpitation in the second and third year residents appeared to be associated with their participation in the surgical pathology rotation, which had not been assigned to the first year residents. In surgical pathology, they had to prepare frozen tissue sections, and it was common practice to "speed up" the work of the cryostat machine by first spraying the tissue with an aerosol preparation consisting of 100% fluorocarbon-22, chosen because it was considered nontoxic.

In their cross-sectional prevalence study, Speizer et al. (27) interviewed employees of a radiology department at another hospital as a control group to compare the prevalence of palpitation with that in members of the pathology department. Before employment, 11% of the members of the pathology department had experienced palpitation, compared with 9% of the members of the radiology department ($p =$ not significant). After employment, 28% of those in the pathology department reported palpitation, compared with 14% in the radiology department ($p < 0.02$). The investigators found a dose-response effect between the number of frozen sections prepared and presence of palpitation.

On basis of these observations, it would seem prudent that workers using fluorocarbons reassess the need for these agents and seek suitable substitutes. For the pathologist or electron microscopist who works in relatively cramped and often poorly ventilated quarters, possible alternatives to fluorocarbons as well as greater attention to proper ventilation should be explored (27).

Carbon monoxide. During the late 1960s, on the basis of experimental studies in rabbits (28) and on studies of carboxyhemoglobin levels in people with Buerger's disease (29), Åstrup and co-workers suggested that carbon monoxide might play an important role in the development of cardiovascular disease. The earliest systematic study (30) on the relation between occupation-associated carbon monoxide exposure and myocardial disease deals with Shinshu myocarditis. Villagers in the Shinshu district of Japan manufactured mats during the winter. They worked in closed, crowded rooms with the windows and crevices sealed and heat provided by an open charcoal fire. Carboxyhemoglobin levels (normally less than 5%) reached a maximum of 20 to 30%. Toward the end of the winter, the frequency of angina-like attacks among these workers was high, and cardiac enlargement, electrocardiographic abnormalities and

decreases in muscular strength and pulmonary vital capacity became evident.

Motor vehicle exhaust fumes are a major source of carbon monoxide. A retrospective study (31) of patients with myocardial infarction admitted to Los Angeles area hospitals indicated that the case fatality rate is increased in areas with high levels of carbon monoxide pollution. In that report, ambient carbon monoxide levels greater than 8 parts per million were associated with significantly increased mortality after myocardial infarction.

Exposure to carbon monoxide occurs in fire fighters (32,33), coal workers, vehicle tunnel workers and freeway travelers (34). Although a few reports (32,33) have implicated carbon monoxide exposure as a cause of increased cardiovascular mortality, these studies are hampered by many confounding factors and serious design limitations. More research, particularly regarding epidemiologic aspects, is needed in this area.

Trace Metal Exposure

Most studies in the field of trace metal exposure lack the experimental rigor necessary to draw meaningful conclusions (35).

Cobalt. In the early 1960s, certain beer brewers in the United States and Canada began adding cobalt to stabilize the foam. Soon afterward, an epidemic of clinically distinct cardiomyopathy occurred. The clinical syndrome was also characterized by polycythemia, pericardial effusion and thyroid hyperplasia. The heart of victims at autopsy contained 10 times more cobalt than normal (36). It seems that three conditions were implicated in this syndrome: alcohol, cobalt and a protein-poor diet (37). Beer drinkers who developed the syndrome were also suffering from inadequate food intake, whereas others, who drank equal amounts of the same beer but who ate normally, remained well.

In 1972, a case of cardiomyopathy accompanying industrial cobalt exposure was reported (38). In the worker who died, there was no indication of excessive alcohol intake nor of an inadequate diet.

Antimony. Antimony has been used in the manufacture of abrasives. Brieger et al. (39) initiated a study of exposure to antimony trisulfide after 8 of 125 workers died from cardiovascular disease within a 2 year period. Six died suddenly and two had long-standing heart disease. In 1954, they reported that among workers exposed to this metal, 37 of 75 men had an abnormal electrocardiogram (mostly T wave abnormalities) (39).

Lead. Since 1975, it has been well documented that occupational exposure to lead can cause chronic nephropathy (40). Accordingly, it was suspected that lead was associated with the presence of hypertension among workers exposed to lead. In a British study (41), lead levels in blood were examined in 135 hypertensive patients and in 135 age-

and sex-matched normotensive subjects. Among hypertensive men, a significant excess of individuals with high blood lead levels was found, with a similar trend among hypertensive women (41). However, an industry-sponsored mortality study (42) of lead workers in lead production facilities and battery plants noted that both the overall mortality and the number of cardiovascular deaths were approximately equal to those expected in the general population.

Cadmium. Although an association has been reported between cadmium exposure and hypertension (43,44), this finding has not been universal (45). In one study (43), untreated hypertensive patients were found to have an average blood cadmium level of 11.1 ng/ml compared with 3.4 ng/ml in normotensive control subjects. All normotensive subjects had blood cadmium levels below 8.0 ng/ml, while in 13 of the 17 hypertensive patients these levels were greater than 8.0 ng/ml.

In experimental studies (46,47), systolic hypertension in rats has been found either by introducing trace amounts of cadmium acetate in the drinking water for 30 months (46) or by injecting small doses of cadmium acetate intraperitoneally (47). Despite these experimental data, the controversy continues regarding the role of cadmium in the etiology of hypertension.

Arsenic. In 1900, beer was accidentally contaminated with arsenic in Manchester, England. More than 6,000 people became ill and 70 died, nearly all from cardiovascular causes (48). Although arsenic was previously considered to be a possible etiologic factor in the increase in coronary artery disease among cigarette smokers (49), arsenic levels in cigarette smoke have become much lower since tobacco growers stopped using insecticides containing arsenic. In a case control study involving a copper smelting operation in Sweden (50), the rate of cardiovascular mortality among workers exposed to arsenic, sulfur dioxide and copper was shown to be 2.1 times greater than that among control subjects, and a dose-response relation to arsenic was demonstrated.

Physical Stress

Noise. It is likely that more than 30 million workers in the manufacturing and electrical utility industries in the United States are exposed to high noise levels on a regular or intermittent basis. The relation between noise-induced hearing loss and hypertension has been disputed. In a Swedish study (51), both systolic and diastolic blood pressure levels were significantly higher in 44 male industrial workers with noise-induced auditory impairment, than in 74 men of the same age who had normal hearing. Other investigators (52,53), however, have not found such a close association between noise and blood pressure level. Carefully controlled investigations are therefore needed to study the effects of high noise levels on industrial workers.

Heat stress. Athletes, military personnel and foundry workers are subjected to heat stress at various times during their work experience. In general, individuals with a healthy cardiovascular system experience little difficulty in heat acclimatization if they have sufficient time to adjust, adequate fluid intake and a slow pace of activity. The effect of long-term exposure to heat stress on the pathogenesis of cardiovascular disease has not been carefully investigated (54).

Radiofrequency radiation. With the proliferation of radar installations and the increasing domestic use of microwave ovens, the amount of exposure to electromagnetic wave radiation has increased considerably. The effects of radar on the health of U.S. Navy personnel were studied (55) in cohorts of approximately 20,000 men with maximal opportunity for exposure (repair of electronic equipment) and 20,000 with minimal potential for exposure (equipment operation) during the Korean War. From 1950 to 1954, no adverse effects on mortality were detected as assessed from data on cause of death, hospitalization during military service, later hospitalization in Veterans Administration (VA) facilities and VA disability compensation.

In Russia, there was a highly publicized and unusually large radiofrequency radiation exposure in individuals at the United States embassy after the deliberate beaming of microwaves into the building (56). A study (57) of embassy personnel concluded that "no convincing evidence was discovered that would directly implicate the exposure to microwave radiation experienced by the employees at the Moscow embassy in the causation of any adverse health effects."

Most of the current scientific information concerning the effects of microwave exposure is derived from Eastern European studies. Hypertension, bradycardia and chest pain have been noted (58). Potential noncardiovascular associations include cataracts, mental and behavioral changes, malignancies and congenital anomalies (59).

Lifestyle Stress

Lifestyle stress is a pervasive phenomenon that is difficult to attribute to any particular occupation or to any particular group of workers within an occupation. People who develop cardiovascular disease can usually relate their illness retrospectively to one or more especially severe psychosocial stresses.

An interesting study was published in 1958 (60) concerning cardiovascular changes in tax accountants who are subject to marked cyclic variation in their occupational stress. Total cholesterol levels and Lee-White clotting times were serially monitored from January through June. The average cholesterol level rose from 210 mg/100 ml during the lull to 252 mg/100 ml at peak stress. The average Lee-White clotting time decreased approximately 30% during the period of peak stress. These data indicate that during peak stress, both cholesterol levels and blood coagulability in-

creased. There appeared to be no confounding effects of changes in weight, diet or exercise during this study (60).

Data concerning work activity level and cardiovascular disease mortality are conflicting. In one study (61), the role of physical activity was assessed in more than 6,000 long-shoremen. The adjusted coronary death rate for the high activity category was 26.9 per 10,000 work-years, while for the medium and low activity categories the rates were 46.3 and 49.0, respectively. An apparent protective threshold effect was seen, especially for the sudden death syndrome, in which the death rate for high activity workers was 5.6 per 10,000 work-years, compared with 19.9 for moderate activity workers and 15.7 for low activity workers. These investigators concluded that repeated bursts of high energy demands establish a plateau of protection against mortality from coronary artery disease. The protective effect of physical activity during work had been noted in previous studies of London busmen (62), American railroad workers (63) and American farmers (64).

The effects of occupation and education on coronary heart disease were examined among workers in the Bell Telephone System (65). The 270,000 men employed at the Bell system operating companies served as the population base for these investigations. Among workmen in the 60 to 64 year age group, the annual rate of first events of disabling coronary disease was 16/1,000 compared with a rate of 10/1,000 among managers and executives. The findings were also stratified according to the subjects' educational background. The annual rate of first events of disabling coronary disease was 16/1,000 among workers without a college education compared with 10/1,000 among those who had gone to college; death rates from coronary disease were 9/1,000 and 6/1,000, respectively. Similar differences were apparent for men in their 40s and 50s.

Conclusions

The main issue underlying the problem of occupation-associated cardiovascular disease is the relation between cause and effect. The finding of an association between a particular occupation and an increase in cardiovascular disease does not necessarily implicate that occupation as the cause of an increase in relative risk. Where not already instituted, close surveillance of workers exposed to unusually high concentrations of inhalants, trace metals and undue physical stress is warranted. Careful studies are needed to account for potential confounding factors such as baseline differences in blood pressure, cigarette smoking habits, age, diabetes and family history of coronary disease. For most occupations, the "healthy worker effect" selects workers who are at lower risk for premature death than the overall population. Future studies should place more emphasis on investigating the health status of retired workers. If a relation between cause and effect can be established for cardiovas-

cular disease within a particular industry, long-term efforts can then be directed toward decreasing specific occupational sources of cardiovascular morbidity.

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